Efficacy of Varenicline in Patients With Severe Alcohol Dependence

A Pilot Double-Blind Randomized and Controlled Study

Philippe Pfeifer, MD and Christoph Fehr, MD†‡*

Abstract:

Purpose/Background: Varenicline has proven its efficacy in the treatment of nicotine dependence, and there is also evidence that it could be helpful in the treatment of alcohol dependence. In our pilot study, we investigated the feasibility and acceptability of varenicline for the treatment of a population of patients with severe alcohol dependence and multiple somatic comorbidities after alcohol detoxification.

Methods/Procedures: We conducted a phase II, double-blind, placebo-controlled randomized trial of daily oral varenicline versus a placebo in alcohol-dependent men and women after alcohol detoxification (n = 28). Following our study protocol, somatic conditions and adverse events were thoroughly monitored and several study end points were investigated (percentage of abstinent days for both alcohol and nicotine, number of standardized drinks and cigarettes per day, days of heavy drinking).

Findings/Results: Compared with the placebo, varenicline did not have more side effects and did not provoke more adverse events. Patients in the varenicline group did not show a significantly higher percentage of alcohol abstinent days or fewer heavy drinking days. A trend significance was found for a reduced number of standard drinks per day ($P = 0.06$) in the varenicline group.

Implications/Conclusions: In this pilot trial, varenicline was shown to be well tolerated by our study population of severely alcohol-dependent patients with somatic conditions. Varenicline did not sustain alcohol abstinence or reduce the number of heavy drinking days, but it did reduce the daily amount of alcohol consumed.

Key Words: varenicline, alcohol dependence, relapse prevention, nicotine abstinence

(*J Clin Psychopharmacol* 2019;00: 00–00)

Alcohol dependence is one of the most disabling conditions worldwide, leading to severe mental and somatic decline.[1] Up until now, less than 20% of patients have received an approved treatment.[2] Hence, the opioid antagonist naltrexone and the glutamate antagonist acamprosate have been approved by the Food and Drug Administration and in Europe for relapse prevention in alcohol dependence.[3] An interesting substance, among others, for the treatment of alcohol dependence is the partial α4β2 nicotine acetylcholine receptor agonist varenicline.[4] Varenicline is a Food and Drug Administration–approved substance for the treatment of nicotine dependence and has been shown to be highly efficient and safe in terms of relapse prevention in smoking.[5] Therefore, varenicline could be of interest in the treatment of patients with alcohol dependence, as animal models have shown modulation in the ventral striatal dopamine system in response to varenicline.[6] There is growing evidence that nicotine acetylcholine receptors, which are located in the ventral tegmental area of the brain, modulate striatal dopamine pathways and therefore may have a blunting effect on the rewarding effects of alcohol intake.[7] In animal studies, the acute administration of varenicline reduced alcohol seeking and voluntary intake in animals exposed chronically to alcohol compared with the administration of a placebo.[8,9]

In humans, clinical trials concerning varenicline's effect on alcohol and nicotine consumption have been conducted on heterogenous groups of clinical populations.[10] In a group of nicotine-dependent patients who were in stable recovery from alcohol dependence, varenicline promoted smoking abstinence without enhancing relapses in alcohol drinking.[11] In another group, varenicline reduced cravings for alcohol, the number of heavy drinking days, the voluntary intake of alcoholic drinks, and the subjective rewarding effects of alcohol.[12] In moderate- and heavy-drinking patients with alcohol dependence, varenicline had no effect on alcohol drinking compared with a placebo, but improvements in mood and alcohol cravings were noticeable.[13] In a large clinical sample of heavy-drinking outpatients with alcohol dependence, varenicline significantly reduced alcohol intake and craving in smokers and nonsmokers alike.[14] Larger randomized trials involving outpatients with alcohol dependence and current alcohol consumption did not find an effect of varenicline on reducing heavy drinking days.[15,16]

The aforementioned studies on the effects of varenicline on nicotine and alcohol consumption were performed predominantly on alcohol-dependent outpatients without comorbidities. In addition, concerns about the safety of varenicline in patients with cardiovascular or neuropsychiatric conditions have been raised.[17] Therefore, in our preliminary trial, we focused our investigation on the safety of varenicline for a group of patients with severe alcohol and nicotine dependence and organic comorbidities after detoxification. Furthermore, several outcome measures on drinking and smoking were assessed during the 12-week trial.

MATERIALS AND METHODS

Study Procedure

We conducted a phase II, double-blind, placebo-controlled randomized trial of daily oral varenicline for patients with alcohol and nicotine dependence. The investigation was conducted in the Departments of Psychiatry and Psychotherapy of the Mainz University Medical Centre and the AGAPLESION Markus Hospital in Frankfurt am Main, Germany. The study was an investigator-initiated trial at the University Medical Center Mainz. Pfizer Germany supported the investigator-initiated trial through a study grant and the provision of the varenicline/placebo medication but was not involved in conducting the study, data analyses, or publication.

From the *Hospital of Psychiatry Muensingen and University Hospital of Psychiatry Bern, Bern, Switzerland; †Department of Psychiatry, Psychotherapy and Psychosomatics, Agaplesion Markus Hospital; and ‡Department of Psychiatry, Psychotherapy and Psychosomatics, University Medical Centre of Frankfurt, Frankfurt am Main, Germany.

Received December 4, 2018; accepted after revision April 17, 2019.

Reprints: Philippe Pfeifer, MD, Psychiatriezentrum Münsingen, Hunzigenallee 1, 3110 Münsingen, Switzerland (e-mail: Philippe.Pfeifer@pzmag.ch).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001056

The study protocol as well as the procedures and materials were approved by the ethics commission of the State Chamber of Medicine in Rheinland-Palatinate, Mainz, and the mandatory German regulatory authorities (Bundesinstitut für Arzneimittel, Bonn). The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Participants

The study participants were recruited in the psychiatric clinics mentioned previously and by public announcement. The study participants were not paid for their participation. To be included, the participants had to fulfill the criteria for alcohol and nicotine dependence listed in the *Diagnostic and Statistical Manual for Mental Disorders* (Fourth Edition). We included man and women between 18 and 65 years of age who had completed alcohol withdrawal therapy successfully. Each participant had last consumed alcohol between 7 and 21 days before the baseline study visit. Participants' motivations for joining the study were assessed by study investigators who had been trained to perform short motivational interventions. Only participants who clearly stated a motive to abstain from alcohol were included. The motivation to quit smoking was not an inclusion criterion. At the time of study inclusion, participants could be either inpatients or outpatients. All inpatients were discharged from inpatient care between 2 to 7 days after randomization.

Main Exclusion Criteria for the Study

Any participant with comorbid substance dependence and psychiatric comorbidities demanding treatment, including schizophrenia, bipolar disorder, major depression, and anxiety; with suicidal ideation as well as a suicidal attempt in their history; and who was being treated with one of the following substances at the time of the screening visit: antipsychotics, antidepressants, mood stabilizers, substances for treatment of alcohol dependence, benzodiazepines, and opioid analgetics was excluded. Furthermore, subjects with the following diseases were excluded: cardiac or brain ischemia; malignancy in the past 5 years; cirrhosis of the liver; acute heart, kidney, or liver diseases; and acute infectious diseases. Finally, any subject who had epileptic seizures or deliriant symptoms during their completed withdrawal episode was excluded.

Study Design

After giving written informed consent, study participants underwent a baseline visit where inclusion and exclusion criteria were checked. Three to 7 days later, the participants who met the inclusion criteria were randomized into the study groups (varenicline vs placebo). At the screening and the baseline visits, all participants were instructed to abstain from alcohol. After randomization, 6 additional visits (in weeks 2, 4, 6, 8, 10, and 12) and 1 telephone visit (week 1) were conducted. After completion of the study, one follow-up visit approximately 2 weeks after the last visit was completed. In any case of a severe drinking relapse, inpatient detoxification was advised. In case of an emergency, written instructions and a telephone number were given to the study participants. The following variables were measured during each study visit: weight, vital signs, breath alcohol concentration, urine drug screening, breath carbon monoxide (CO) concentration and medical management. Electrocardiogram and routine laboratory (liver enzymes, basic hematology, blood minerals, creatinine, carbohydrate-deficient transferrin) examinations were conducted every 3 weeks. During each study visit, we measured the amount of plasma γ-glutamyltransferase (GGT) as a parameter for alcohol consumption and CO as a parameter for smoking. Female participants underwent a pregnancy test at baseline, at visits 2 and 6, and in any case of suspected pregnancy. Each study participant was examined by the responsible study investigator for adverse effects (AEs) during each study visit.

Administration of Study Medication

The study medication was administered orally, with the doses of varenicline ranging from 0.5 mg at the beginning of the study to 1.0 mg after day 7 of the study. The same medication protocol was observed for both groups: in the first 3 days of the study, both study groups received one tablet in the morning (0.5 mg varenicline or the placebo). From days 4 to 7, all participants received 2 tablets per day, one in the morning and one at noon (2×0.5 mg varenicline or the placebo). From day 8 until the end of the study, each participant received 2 tablets per day, one in the morning and one at noon (2×1.0 varenicline or the placebo). Therapy adherence was monitored during the regular study visits. At each study visit, the participants received the exact amount of medication needed until the next study visit, including instructions for intake. The participants were asked to return a blister that was checked for correct intake, and they had to report tablet intake at each visit.

Assessment of Clinical Parameters

Drinking behavior was assessed via the time line followback method.[18] During each study visit, the participants reported on their daily drinking amounts as well as number of cigarettes per day since the last study visit (for the last 90 days before the screening visit). Subjective responses (eg, 1 L of beer) were converted into the number of standard drinks (eg, 4 standard drinks). One standard drink indicated 12 g of alcohol. Severity and length of alcohol dependence were assessed using the European Addiction Severity Index.[19] Severity of nicotine dependence was assessed by using the Fagerstrom Test for nicotine dependence.[20] Depressed mood was assessed by using the Hamilton Depression Scale and the Beck Depression Inventory at each study visit.[21,22] Subjects who scored higher than 12 on the Hamilton Depression Scale or 9 on the Beck Depression Inventory were considered to be depressed and excluded from the study. Alcohol craving was measured using the Obsessive Compulsive Drinking Scale.[23]

Study End Points

The primary end point was defined as the percentage of days without alcohol consumption during treatment. In addition, a deduced percentage of abstinent days was calculated by defining undocumented days (eg, after early study termination) as days with alcohol consumption. The main secondary end points were as follows: (i) number of standardized drinks during treatment, (ii) percentage of heavy drinking days, (iii) number of cigarettes per day, and (iv) percentage of nicotine abstinence days. Safety end points comprised adverse events (coded according to MedDRA 17.0), concomitant medication, and psychiatric assessment. Adverse effects comprised neuropsychiatric as well as gastrointestinal, dermatologic, and allergic side effects.

Statistical Analyses

Details of the statistical analysis were documented in a Statistical Analysis Plan that was finalized before closing the database. The Statistical Analysis Plan was based on the protocol, including all amendments. Analyses of primary and secondary end points were based on the intention-to-treat population comprising all randomized patients. The primary analysis compared the rate of alcohol abstinence days between treatment groups using an

analysis of variance with the treatment as a fixed effect (2-sided, $\alpha = 5\%$). All secondary end points were analyzed on an exploratory basis using appropriate tests that depended on the scale of the parameter. Fisher exact test was used to analyze the number of patients with sustained abstinence in terms of alcohol consumption. The percentage of heavy drinking days and the percentage of nicotine abstinent days were analyzed using the *t* test. The Wilcoxon rank sum test and Wilcoxon sign rank test were used to analyze the number of standardized drinks and number of cigarettes per day, respectively. Cohen *d* was used to calculate the effect size for the reduced standard drinks and cigarettes. Cohen *d* is an effect size that is used to indicate the standardized difference between 2 means. An effect size smaller than 0.5 is termed small, an effect size between 0.5 and 0.8 is considered to be medium and an effect size greater than 0.5 is thought of as large.[24] The time to first serious drinking was estimated using Kaplan-Meier and the corresponding log-rank test. For the analysis of changes in biomarkers, we performed an analysis of covariance test with GGT and CO as the dependent variables, and the covariables were varenicline and placebo group and changes to baseline.

RESULTS

Sample Population and Clinical Characteristics

From July 2010 to July 2013, we recruited 28 subjects. Fifteen subjects were randomized to the varenicline group, and 13 subjects were randomized to the placebo group. The demographic variables and the histories of alcohol and nicotine dependence are shown in Table 1.

Considering all the participants, 20.0% (n = 3) from the varenicline group completed the trial following the regular protocol, whereas none from the placebo group managed to do so. The reasons for dropping out of the study included a lack of motivation and time and alternative therapy options, among others. Two subjects from the varenicline group dropped out because of adverse effects (increased body temperature, fatigue) despite a low therapeutic dose (0.5 mg/d). The number of AEs was comparable in both groups (varenicline, n = 62; placebo, n = 55). There were no significant differences in the AEs in the neuropsychiatry, allergy, and dermatology categories. Subjects in the varenicline group had a slightly higher risk for nausea (8.1%) compared with the placebo group (1.8%). The overall therapy adherence was 88.5% (±23.0%; $P = 0.76$).

Study End Points

The primary and secondary end points of the intention-to-treat analyses are presented in Table 2. With regard to the primary end point, which was defined as the rate of abstinent days within the 12-week period of treatment, no statistically significant difference between the 2 groups was found ($P = 0.58$). The mean (SD) percentage of abstinent days in the varenicline group was 83.3% (24.1%) compared with 87.9% (15.4) in the placebo group.

The participants consumed an overall average (SD) of 21.5 (11.9) standardized drinks per day in the 90 days before randomization (varenicline: 21.0 [12.1], $P = 0.12$; placebo: 22.1 [12.2], $P = 0.68$). During the treatment, we observed a reduction in standardized drinks per day in the varenicline group, with a total mean (SD) number of 11.4 (12.2) drinks per day ($P = 0.06$; $d = 0.79$). In the placebo group, we observed a reduction 1.3 drinks, on average, with a total mean (SD) number of 21.0 (11.9) drinks per day ($P = 0.44$, $d = 0.09$). Although the reduction was somewhat greater in the varenicline group, the difference in reduction between the groups did not reach statistical significance ($P = 0.17$, Table 2). The percentages of heavy drinking days during the study for the 2 groups were not significantly different (varenicline: 10.6%; placebo: 10.8%, $P = 0.98$). During the course of the study, the plasma GGT decreased in both groups. Carbohydrate-deficient transferrin decreased in both study groups from 2.86% to 1.67% (mean) in the varenicline group and from 3.38% to 1.73% (mean) in the placebo group.

With regard to nicotine dependence, at the beginning of the study, most of the participants were moderately to severely dependent (Fagerstrom test mean (SD) score, 5.6 [2.9]). There was no statistical difference between both groups. The number of cigarettes per day showed a mean (SD) of 18.1 (9.5) in the varenicline group

TABLE 1. Demographic Data and History of Alcohol and Nicotine Abuse—ITT Population (n = 28)

	Varenicline (n = 15)	Placebo (n = 13)	Total (n = 28)
Age, mean (SD), y	45.73 (9.27)	44.15 (6.84)	45.00 (8.12)
Sex			
Female	2 (13.33%)	2 (15.38%)	4 (14.29%)
Male	13 (86.67%)	11 (84.62%)	24 (85.71%)
No. years with problematic alcohol consumption*			
n	15	13	28
Mean (SD)	12.27 (7.84)	16.08 (8.91)	14.04 (8.42)
No. years with alcohol dependence*			
n	15	13	28
Mean (SD)	9.00 (5.93)	11.46 (8.98)	10.14 (7.46)
No. withdrawal therapies			
n	15	13	28
Mean (SD)	8.33 (10.71)	3.54 (3.28)	6.11 (8.38)
Median	4	3	3
Started to smoke (age in years)†			
n	15	13	28
Mean (SD)	18.07 (6.81)	18.54 (3.07)	18.29 (5.32)

*European Addiction Severity Index.

†Fagerstrom Test for Nicotine Dependence.

TABLE 2. Primary and Secondary Therapy End Points—ITT Population (n = 28)

	Varenicline (n = 15)	Placebo (n = 13)	*P**
Percentage of abstinent alcohol days after randomization, percent (SD)	83.3 (24.1)	87.9 (15.4)	0.58[†]
Standard drinks per day			
Before treatment, mean (SD)	21.0 (12.1)	22.1 (12.2)	0.68[‡]
After randomization, mean (SD)	11.4 (12.2)	21.0 (11.9)	0.12[‡]
Reduction in the standard drinks per day			
No.	−11.3 (11.1)	−1.3 (9.1)	0.17[‡]
Wilcoxon rank sum test	$P = 0.06$	$P = 0.44$	
Percentage of nicotine abstinence days after randomization, percent (SD)	5.4 (17.8)	0.7 (2.3)	0.40[§]
No. cigarettes per day			
Before treatment, mean (SD)	26.2 (13.4)	25.9 (10.2)	0.73*
After randomization, mean (SD)	18.1 (9.5)	20.5 (10.4)	0.49*

*$P < 0.05$ indicates a significant difference between groups.

[†]Analysis of variance.

[‡]Wilcoxon rank sum test.

[§]*t* Test.

compared with 20.5 (10.4) in the placebo group, but there was no significant difference in cigarette consumption ($P = 0.49$). Compared with the mean number of cigarettes per day at baseline (varenicline: mean [SD], 26.2 [13.4]; placebo: mean [SD], 25.9 [10.2]), a statistically significant reduction was observed in both groups (varenicline, $P = 0.001$; placebo, $P = 0.001$). However, there was no statistically significant difference between the 2 groups ($P = 0.23$). The percentage of nicotine abstinence days in the varenicline group (5.4% [17.8%]) was slightly higher than that in the placebo group (0.7% [2.3]), but the difference was not statistically significant ($P = 0.4$). Carbon monoxide values decreased significantly in both groups compared with baseline ($P < 0.0001$), but no difference was observed between the varenicline and the placebo groups ($P = 0.60$). Alcohol craving (Obsessive Compulsive Drinking Scale score) was comparable in both groups at baseline (varenicline: mean [SD], 9.4 [6.5]; placebo: mean [SD], 12.9 [9.6]). During the treatment, a mean reduction in craving was found in both groups at the end of the study (mean scores, 4.2 for varenicline and 5.5 for placebo).

DISCUSSION

In this preliminary trial, we tested the acceptability and efficacy of varenicline in a cohort of detoxified patients with severe alcohol dependence. With regard to the primary end point, that is, the percentage of abstinent days for alcohol, varenicline did not show a significant effect compared with placebo. In the varenicline group, there was a trend toward a reduction in the number of daily standard drinks consumed.

There has been a controversial discussion of varenicline in the literature with regard to neuropsychiatric syndromes and cardiovascular diseases.[5,25] In our study sample of severely ill patients, the AEs and dropout rates due to the pharmacological adverse effects of varenicline were not higher than the dropout rates for the placebo group. Therefore, our results confirm the results of a recently published trial that showed no increase in neuropsychiatric AEs in psychiatric and nonpsychiatric patients.[26]

Several studies have investigated the effect of varenicline on drinking parameters in alcohol use disorders previously.[14–17,26,27] Our finding that varenicline had no effect on alcohol abstinence corresponds to the results of 3 other studies.[14–16] Otherwise, our study confirms the finding of 2 previous studies that varenicline reduces the daily alcohol intake but has no positive effect on heavy drinking days.[12,15] It is noteworthy that our study participants consumed about twice the mean dose of alcohol per day compared with participants in the study by Litten et al.[15] Although the findings in our study were not statistically significant, there was a medium effect size for the reduction of daily alcohol intake in the varenicline group. There were no effects of varenicline on alcohol cravings in our study. This finding corresponds to previous studies that found no or only small effects of varenicline in reducing alcohol craving.[12,27] However, in contrast to our participants, the latter study samples consisted mainly of heavy-drinking smokers seeking treatment of smoking. Furthermore, patients in our investigation underwent detoxification before treatment and may have experienced stronger cravings than those patients not undergoing withdrawal.

We found only a modest reduction in smoking for the subjects taking varenicline, despite the fact that the latter is well established as a pharmacological treatment of nicotine dependence.[27] In contrast, other studies found a positive effect of varenicline on nicotine consumption in heavy-drinking subjects and a positive correlation between the reduction in cigarette smoking and the consumption of alcohol.[17,26] However, that some participants in our study had no explicit aim to quit smoking may explain the reduced efficacy of varenicline in reducing smoking.

We recognize the limitations of our study: because of a restrictive approach with multiple exclusion criteria, we were not able to recruit more study participants. Our study results are limited to a small sample size and should be perceived of as preliminary. However, a real drug-placebo difference cannot be excluded and may be obscured by the small number of subjects and the high variability present. Another limitation is the low retention rate of participants in the study. This low retention may be due to the severity of the dependence, leading to a higher frequency of drinking relapses of stronger severity.

In summary, varenicline was safe and well tolerated in a naturalistic clinical population of patients who were severely affected by alcohol dependence as well as by other comorbidities. Although varenicline was effective in reducing the number

of standard drinks per day, it failed to prove effective in other measures of alcohol and nicotine consumption.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflict of interest.

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